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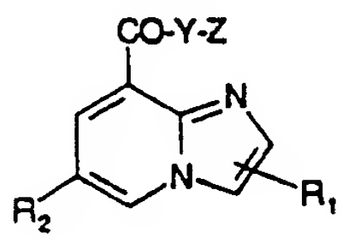

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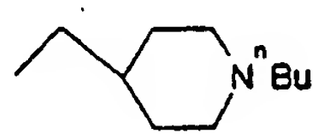

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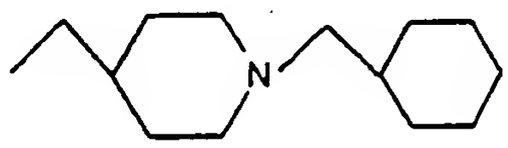

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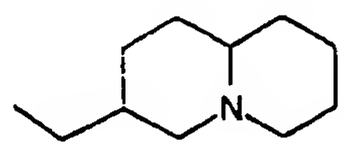

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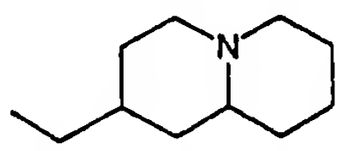

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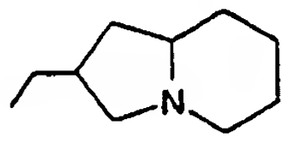

(v)

(57) Abstract

Compounds of formula (I), and pharmaceutically acceptable salts thereof, and the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein R_1 is hydrogen or C_{1-6}alkyl; R_2 is hydrogen or halo; Y is O or NH; Z is of sub-formula (i), (ii), (iii), (iv) or (v), or wherein the piperidine ring in (i) or (ii) is replaced by pyrrolidinyl and/or the N-substituent in (i) or (ii) is replaced by R_3 wherein R_3 is hydrogen or C_{1-12}alkyl, aralkyl or R_3 is $(CH_2)_r$-R_{10} wherein r is 2 or 3 and R_{10} is selected from cyano, hydroxyl, C_{1-6}alkoxy, phenoxy, $C(O)C_{1-6}$alkyl, COC_6H_5, -$CONR_{11}R_{12}$, $NR_{11}COR_{12}$, $SO_2NR_{11}R_{12}$ or $NR_{11}SO_2R_{12}$ wherein R_{11} and R_{12} are hydrogen or C_{1-6}alkyl; or a compound of formula (I) wherein the CO-Y linkage is replaced by a heterocyclic bioisostere; having 5-HT_4 receptor antagonist activity.

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Imidazopyridine derivatives as 5-HT4 receptor antagonists

This invention relates to novel compounds having pharmacological activity, to a process for their preparation and to their use as pharmaceuticals.

European Journal of Pharmacology 146 (1988), 187-188, and Naunyn-Schmiedeberg's Arch. Pharmacol. (1989) 340:403-410, describe a non classical 5-hydroxytryptamine receptor, now designated the 5-HT_4 receptor, and that ICS 205-930, which is also a 5-HT_3 receptor antagonist, acts as an antagonist at this receptor.

WO 91/16045 (SmithKline and French Laboratories Limited) describes the use of cardiac 5-HT_4 receptor antagonists in the treatment of atrial arrhythmias and stroke.

EP-A-501322 (Glaxo Group Limited) describes indole derivatives having 5-HT_4 antagonist activity.

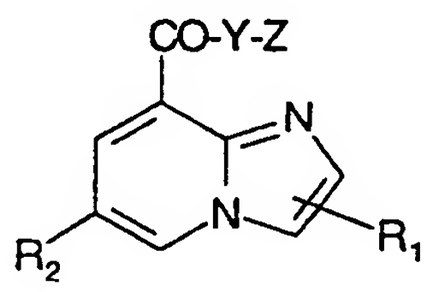
WO 93/02677, WO 93/03725, WO 93/05038, WO 93/05040 and PCT/GB93/00506 (SmithKline Beecham plc) describe compounds having 5-HT_4 receptor antagonist activity.

EP-A-504679 (G.D. Searle & Co.) describes 5-HT_3 receptor antagonists with *inter alia*, an imidazopyridine nucleus.

A class of novel, structurally distinct compounds has now been discovered, which compounds are imidazopyridinyl derivatives with an azacyclic, fused azabicyclic or aminoalkyl moiety. These compounds have 5-HT_4 receptor antagonist activity.

When used herein, 'treatment' includes prophylaxis as appropriate.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

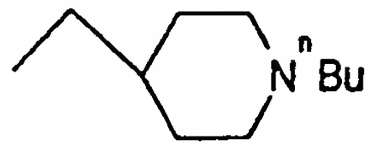
wherein

R_1 is hydrogen or C_{1-6} alkyl;

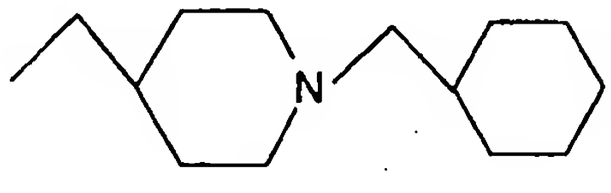
R_2 is hydrogen or halo;

Y is O or NH;

Z is of sub-formula (i), (ii), (iii), (iv) or (v):



(i)



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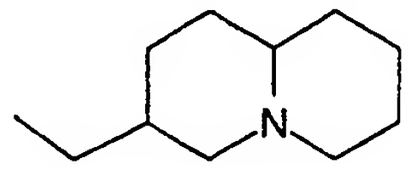

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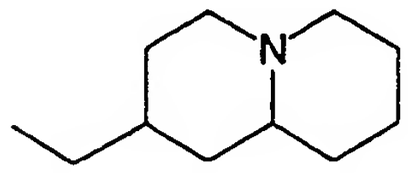

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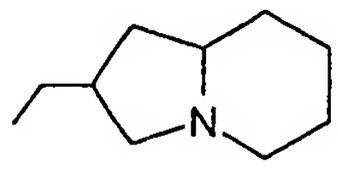


(v)

or wherein the piperidine ring in (i) or (ii) is replaced by pyrrolidinyl and/or the N-substituent in (i) or (ii) is replaced by R_3 wherein

R_3 is hydrogen or C_1-12 alkyl, aralkyl or R_3 is $(CH_2)_r$-R_{10} wherein r is 2 or 3 and

R_{10} is selected from cyano, hydroxyl, C_{1-6} alkoxy, phenoxy, $C(O)C_{1-6}$ alkyl, COC_6H_5, -$CONR_{11}R_{12}$, $NR_{11}COR_{12}$, $SO_2NR_{11}R_{12}$ or $NR_{11}SO_2R_{12}$

wherein R_{11} and R_{12} are hydrogen or C_{1-6} alkyl;

or a compound of formula (I) wherein the CO-Y linkage is replaced by a heterocyclic bioisostere;

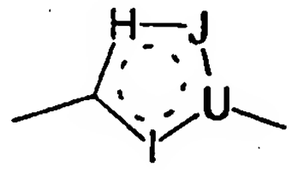
having 5-HT_4 receptor antagonist activity.

Examples of alkyl or alkyl containing groups include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11} or C_{12} branched, straight chained or cyclic alkyl, as appropriate. C_{1-4} alkyl groups include methyl, etnyl *n*- and *iso*-propyl, *n*-, *iso*-, *sec*- and *tert*-butyl. Cyclic alkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

Aryl includes phenyl and naphthyl optionally substituted by one or more substituents selected from halo, C_{1-6} alkyl and C_{1-6} alkoxy.

Halo includes fluoro, chloro, bromo and iodo.

A suitable bioisostere for the amide or ester linkage containing Y in formula (I), is of formula:



wherein

the dotted circle represents one or two double bonds in any position in the 5-membered ring; H, J and I independently represent oxygen, sulphur, nitrogen or carbon, provided that at least one of H, J and I is other than carbon; U represents nitrogen or carbon.

Suitable examples of (d) are as described for X, Y and Z in EP-A-328200 (Merck Sharp & Dohme Ltd.), such as an oxadiazole moiety.

R_1 is preferably hydrogen.

R_2 is preferably hydrogen.

Y is preferably O or NH.

The N-substituent in formula (i) or (ii) may be replaced by optionally substituted benzyl or by $(CH_2)_nR^4$, as defined in formula (I) and in relation to the specific examples of EP-A-501322.

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) such as the compounds quaternised by compounds R_X-T wherein R_X is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_X include methyl, ethyl and *n*- and *iso*-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

Examples of pharmaceutically acceptable salts also include internal salts such as N-oxides.

The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

Azabicyclic values of Z may exist in α and β forms.

The compounds of formula (I) may be prepared by conventional coupling of the moiety with Z. Suitable methods are as described in GB 2125398A (Sandoz Limited), GB 1593146A and EP-A-36269 (Beecham Group p.l.c.). When CO-Y is replaced by a heterocyclic bioisostere, suitable methods are described in EP-A-328200 (Merck Sharp & Dohme Limited). Reference is also made to EP-A-501322 (Glaxo Group Limited).

Imidazopyridine intermediates may be prepared as described in EP-A-504679.

Aza(bi)cyclic side chain intermediates are known compounds or may be prepared according to the methods described in the aformentioned patent publications (SmithKline Beecham p.l.c.).

The compounds of the present invention are 5-HT_4 receptor antagonists and it is thus believed may generally be used in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

They are of potential interest in the treatment of irritable bowel syndrome (IBS), in particular the diarrhoea aspects of IBS, i.e., these compounds block the ability of 5-HT to stimulate gut motility via activation of enteric neurones. In animal models of IBS, this can be conveniently measured as a reduction of the rate of defaecation. They are also of potential use in the treatment of urinary incontinence which is often associated with IBS.

They may also be of potential use in other gastrointestinal disorders, such as those associated with upper gut motility, and as antiemetics. In particular, they are of potential use in the treatment of the nausea and gastric symptoms of gastro-oesophageal reflux disease and dyspepsia. Antiemetic activity is determined in known animal models of cytotoxic-agent/radiation induced emesis.

Specific cardiac 5-HT_4 receptor antagonists which prevent atrial fibrillation and other atrial arrhythmias associated with 5-HT, would also be expected to reduce occurrence of stroke (see A.J. Kaumann 1990, Naumyn-Schmiedeberg's Arch. Pharmacol. 342, 619-622, for appropriate animal test method).

Anxiolytic activity is likely to be effected via the hippocampus (Dumuis *et al* 1988, Mol Pharmacol., 34, 880-887). Activity can be demonstrated in standard animal models, the social interaction test and the X-maze test.

Migraine sufferers often undergo situations of anxiety and emotional stress that precede the appearance of headache (Sachs, 1985, Migraine, Pan Books, London). It has also been observed that during and within 48 hours of a migraine attack, cyclic AMP levels are considerably increased in the cerebrospinal fluid (Welch *et al.*, 1976, Headache 16, 160-167). It is believed that a migraine, including the prodomal phase and the associated increased levels of cyclic AMP are related to stimulation of 5-HT_4 receptors, and hence that administration of a 5-HT_4 antagonist is of potential benefit in relieving a migraine attack.

Other CNS disorders of interest include schizophrenia, Parkinson's disease and Huntingdon's chorea.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are usually adapted for enteral such as oral, nasal or rectal, or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, nasal sprays, suppositories, injectable and infusable solutions or suspensions. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and if

desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment or prophylaxis of irritable bowel syndrome, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine in mammals, such as humans, which comprises the administration of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.05 to 1000mg for example 0.5 to 500mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.0001 to 50mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

No adverse toxicological effects are indicated within the aforementioned dosage ranges.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of irritable bowel syndrome, gastro-oesophageal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine.

The following Examples illustrates the preparation of compounds of formula (I), and the following Description relate to the preparation of an intermediate.

It will be appreciated that any compound prepared wherein Y is O may be provided as the corresponding compound wherein Y is NH or *vice versa*.

Description

a) 2-Amino-5-chloronicotinic acid

To a solution of 2-aminonicotinic acid (g) in acetic acid (50ml) was added a solution of chlorine (2.81g) in acetic acid (44ml). The reaction mixture was stirred at room temperature for 4 days. The solvent was concentrated under reduced pressure and the solid filtered and dried to afford the title compound (4.7g)

^{1}H NMR (250MHz) d_6-DMSO

δ 8.48 (d, 1H), 8.29 (d, 1H)

b) 6-Chloroimidazo[1,2-a]pyridine-8-carboxylic acid

2-Amino-5-chloronicotinic acid (2g) and chloroacetaldehyde (1.83ml) were suspended in ethanol (50ml) and the resulting slurry heated to reflux overnight. The mixture was cooled to room temperature and the solvent concentrated under reduced pressure. The residue was suspended in acetone, filtered and dried to leave 6-chloroimidazo[1,2-a]pyridine-8-carboxylic acid (D1) (1.72g) as an off-white solid.

^{1}H NMR (250MHz) d_6DMSO

δ: 9.58(d, 1H), 8.45-8.52(m, 2H), 8.19(d, 1H)

Examples

Example 1 [R_1 = H, R_2 = Cl, Y = NH, Z = (i)]

(1-Butyl-4-piperidinylmethyl) 6-chloroimidazo[1,2-a]pyridyl-8-carboxamide (E1)

A suspension of 6-chloroimidazo[1,2-a]pyridine-8-carboxylic acid (D1) (250mg) in acetonitrile (10ml) was treated with 1,1'-carbonyldiimidazole (330mg) and the resulting mixture heated gently for 2h. The solution was cooled to room temperature and the solvent concentrated *in vacuo*. To the residue dissolved in N,N'-dimethylformamide (10ml) was added a solution of 1-butyl-4-aminomethylpiperidine (230mg) in N,N'-dimethylformamide (10ml). The resulting mixture was stirred at room temperature and the solid filtered to afford the title

compound (260mg).

^{1}H NMR (250MHz) CD_3OD

δ: 8.67 (d, 1H), 7.77-7.84 (m, 2H), 7.52 (d, 1H), 3.31-3.48 (m, 4H), 2.74-2.97 (m, 4H), 1.83-1.99 (m, 3H), 1.40-1.64 (m, 4H), 1.15-1.44 (m, 2H), 0.83 (t, 3H)

Example 2 [R_1 = H, R_2 = Cl, Y = NH, Z = (iii)]

2-*eq*-Quinolizidin-2-ylmethyl 6-chloroimidazo[1,2-a]pyridyl-8-carboxamide (E2)

Following the procedure outlined in Example 1, *eq*-2-aminomethyl quinolizidine (200mg) gave the title compound as a white solid (260mg).

^{1}H NMR 250MHz (CD_3OD)

δ: 8.83 (d, 1H), 7.95-8.01 (m, 2H), 7.71 (d, 1H), 3.37-3.55 (m,4H), 2.89-3.16 (m, 3H), 1.33-2.19 (m, 11H).

Example 3 [R_1 = H, R_2 = Cl, Y = O, Z = (i)]

(1-Butyl-4-piperidinylmethyl) 6-chloroimidazo[1,2-a]pyridyl-8-carboxylate (E3)

A suspension of 6-chloroimidazo[1,2-a]pyridine-8-carboxylic acid (D1) (250mg) in acetonitrile (10ml) was treated with 1,1'-carbonyldiimidazole (330mg) and the resulting mixture heated gently for 2h. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was suspended in N,N'-dimethylformamide (10ml) and a solution of 1-butyl-4-hydroxymethylpiperidine (230mg) in N,N'-dimethylformamide (10ml) added. The solution was stirred at room temperature overnight. The solvent was concentrated *in vacuo* and the residue partitioned between chloroform and *aq*.K_2CO_3. The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was chromatographed on silica to afford the title compound (130mg).

^{1}H NMR 250MHz ($CDCl_3$)

δ: 8.36 (d, 1H), 7.87 (d, 1H), 7.78 (d, 1H), 7.63 (d, 1H), 4.39 (d, 2H), 3.01 (bd, 2H), 2.34 (dt, 2H), 1.96 (t, 3H), 1.82 (bd, 2H), 1.41-1.59 (m, 4H), 1.27-1.39 (m, 2H), 0.91 (t, 3H).

5-HT_4 RECEPTOR ANTAGONIST ACTIVITY

1) Guinea pig colon

Male guinea-pigs, weighing 250-400g are used. Longitudinal muscle-myenteric plexus preparations, approximately 3cm long, are obtained from the distal colon region. These are suspended under a 0.5g load in isolated tissue baths containing Krebs solution bubbled with 5% CO_2 in O_2 and maintained at 37°C. In all experiments, the Krebs solution also contains methiothepin 10^{-7}M and granisetron 10^{-6}M to block effects at 5-HT_1, 5-HT_2 and 5-HT_3 receptors.

After construction of a simple concentration-response curve with 5-HT, using 30s contact times and a 15min dosing cycle, a concentration of 5-HT is selected so as to obtain a contraction of the muscle approximately 40-70% maximum(10^{-9}M approx). The tissue is then alternately dosed every 15min with this concentration of 5-HT and then with an approximately equi-effective concentration of the nicotine receptor stimulant, dimethylphenylpiperazinium (DMPP). After obtaining consistent responses to both 5-HT and DMPP, increasing concentrations of a putative 5-HT_4 receptor antagonist are then added to the bathing solution. The effects of this compound are then determined as a percentage reduction of the contractions evoked by 5-HT or by DMPP. From this data, pIC_{50} values are determined, being defined as the -log concentration of antagonist which reduces the contraction by 50%. A compound which reduces the response to 5-HT but not to DMPP is believed to act as a 5-HT_4 receptor antagonist.

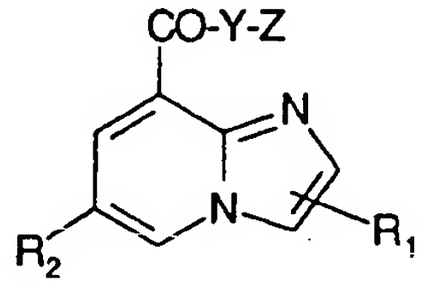
The compounds of the Examples 1 and 3 had a pIC_{50} value of >8, E1 being preferred.

2) Rat oesophagus

Rat oesophageal tunica muscularis mucosae is set up according to Baxter *et. al.* Naunyn-Schmiedeberg's Arch. Pharmacol., 343, 439-446 (1991). The inner smooth muscle tube of the muscularis mucosae is isolated and mounted for isometric tension recording in oxygenated (95% O_2/5% CO_2) Tyrodes solution at 37°C. All experiments are performed in pargyline pre-treated preparations (100μM for 15 min followed by washout) and in the presence of cocaine (30μM). Relaxant responses to 5-HT are obtained after pre-contracting the oesophagus tissue with carbachol (3μM).

Claims

1. Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

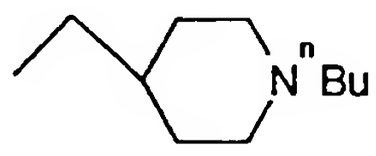
wherein

R_1 is hydrogen or C_{1-6} alkyl;

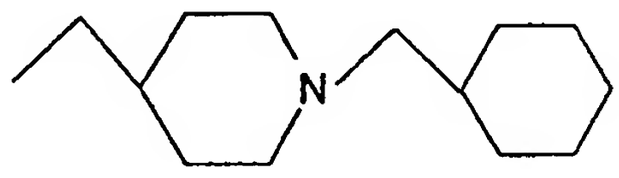
R_2 is hydrogen or halo;

Y is O or NH;

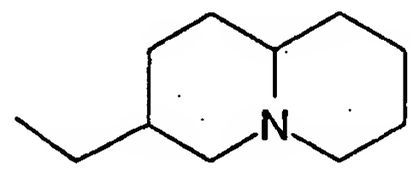
Z is of sub-formula (i), (ii), (iii), (iv) or (v):



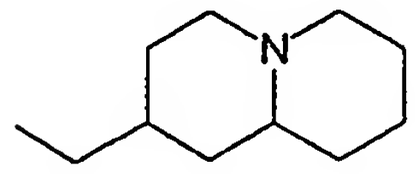
(i)



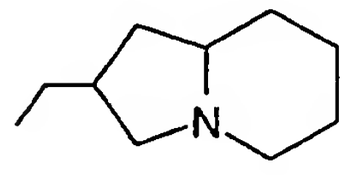
(ii)



(iii)



(iv)



(v)

or wherein the piperidine ring in (i) or (ii) is replaced by pyrrolidinyl and/or the N-substituent in (i) or (ii) is replaced by R_3 wherein

R_3 is hydrogen or C_{1-12} alkyl, aralkyl or R_3 is $(CH_2)_r$-R_{10} wherein r is 2 or 3 and

R_{10} is selected from cyano, hydroxyl, C_{1-6} alkoxy, phenoxy, $C(O)C_{1-6}$ alkyl, COC_6H_5, -$CONR_{11}R_{12}$, $NR_{11}COR_{12}$, $SO_2NR_{11}R_{12}$ or $NR_{11}SO_2R_{12}$ wherein R_{11} and R_{12} are hydrogen or C_{1-6} alkyl;

or a compound of formula (I) wherein the CO-Y linkage is replaced by a heterocyclic bioisostere;

having 5-HT_4 receptor antagonist activity.

2. A compound according to claim 1 wherein R_1 is hydrogen.

3. A compound according to claim 1 or 2 wherein R_2 is hydrogen or chloro.

4. A compound according to claim 1, 2, or 3 wherein Y is O or NH.

5. A compound according to claim 1 wherein The N-substituent in sub-formula (i) or (ii) is be replaced by optionally substituted benzyl or by $(CH_2)_nR^4$, as defined in formula (I) and in relation to the specific examples of EP-A-501322.

6. (1-Butyl-4-piperidinylmethyl) 6-chloroimidazo[1,2-a]pyridyl-8-carboxamide.

7. 2-*eq*-Quinolizidin-2-ylmethyl 6-chloroimidazo[1,2-a]pyridyl-8-carboxamide

8. (1-Butyl-4-piperidinylmethyl) 6-chloroimidazo[1,2-a]pyridyl-8-carboxylate

9. A compound substantially as hereinbefore described with reference to any one of the Examples.

10. A process for preparing the ester or amide compounds (where Y is O or NH) according to claim 1, which comprises reacting an appropriate acid derivative with an appropriate alcohol or amine.

11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9, and a pharmaceutically acceptable carrier.

12. A compound according to claim 1 for use as an active therapeutic substance.

13. The use of a compound according to claim 1 in the manufacture of a medicament for use as a 5-HT_4 receptor antagonist.

14. The use according to claim 13 for use as a 5-HT_4 receptor antagonist in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

INTERNATIONAL SEARCH REPORT

PCT/EP 93/02808

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D471/04 C07D519/00 A61K31/435 //(C07D471/04,235:00, 221:00),(C07D519/00,471:00,455:00),(C07D519/00,471:00,471:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 15593 (G.D.SEARLE) 17 September 1992 cited in the application see page 74; claims 1,22 ---	1,11,13
A	EP,A,0 501 322 (GLAXO) 2 September 1992 cited in the application see claims 1,15 -----	1,11,13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 February 1994	14. 02. 94
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

PCT/EP 93/02808

Box I Observations where certain claims were found unsearchable (Continuation f item 1 f first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 14 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9215593	17-09-92	US-A-	5260303	09-11-93
		AU-A-	1572892	06-10-92
		EP-A-	0504679	23-09-92
		EP-A-	0530353	10-03-93
EP-A-0501322	02-09-92	AU-B-	645402	13-01-94
		AU-A-	1209492	15-09-92
		WO-A-	9214727	03-09-92